World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

The effect of topical saliva application as a factor to accelerate wound healing: A review article

Aishwara Hapsari Putri [1,*], Arnisa Wira Cahyani Sukma [1] and Tantiana [2]

[1] *Faculty of Dental Medicine, Airlangga University, Surabaya, Indonesia.*
[2] *Department of Oral Biology, Faculty of Dental Medicine, Airlangga University, Surabaya, Indonesia.*

World Journal of Advanced Research and Reviews, 2024, 21(03), 1986–1990

Publication history: Received on 02 February 2024; revised on 16 March 2024; accepted on 19 March 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.21.3.0832

Abstract

Background: Saliva is one part of the oral environment that has an important role in maintaining oral tissues. Saliva is also able to stimulate wound healing. When compared to wounds on the skin, the mucosa in the oral cavity tends to heal faster. Saliva is believed to be one of the main factors contributing to this comparison.

Objective: This paper aims to determine the effectiveness of saliva as a factor that accelerates wound healing on topically applied skin.

Methods: A source search of various journals found on internet databases was conducted to obtain relevant information related to this study.

Discussion: Various biological substances contained in saliva, one of which functions in wound healing. The content of histatin and growth factors in saliva is influential in accelerating the wound healing process with the best reconstruction results. Conclusion: Saliva is effective in accelerating wound healing and can stimulate skin wound closure and has the potential to become a new therapy for treating open skin wounds.

Keywords: Saliva; Wound healing; Proliferation; Topical

1. Introduction

Saliva is a watery compound from the body that has crucial function in maintaining oral environment. Physically, saliva has a transparent color with a thick, slippery and slightly sticky texture. Saliva is generated by the salivary glands around the face. The glands are divided into two types, namely major salivary glands (which are parotid, submandibular, and sublingual) and minor salivary glands [1]. Saliva, which is known as a compound that is closely related to the oral cavity, is known to be an indicator of how the condition of the body as a whole. Therefore, saliva is referred to as the 'Mirror of the Body' [2].

Saliva has several important compositions that can work specifically to provide signs or information that something is working incorrectly in the body system. This can happen because in saliva, many other compounds are also contained even if they are not too related to the composition of saliva in general. These compounds can be nasal secretions, derivatives from oral wounds, bacteria, gingival sulcus fluid, viruses, fungi and enzymes. These contents are able to be tested to obtain vital clues of systemic health in the body [3]. The use of saliva in diagnosis is greatly influenced by technological developments, such as hepatitis, HIV, tuberculosis, rubella, and others that manifest systemically or orally. Saliva has a high protein content in its role to be able to heal wounds [4].

* Corresponding author: Aishwara Hapsari Putri

Beside working as an indicator, saliva is also known to contain a large amount of protein and can play a good role in wound healing. Various studies write that wounds that happened in the oral mucosa tend to heal faster and better than wounds on the outer skin [5]. Saliva is considered to be able to accelerate wound healing. Since ancient times, saliva has been a traditional medicine that helps heal external wounds, specifically saliva applied topically on the wound surface. Another form of proof that saliva can affect wounds is available by looking at events around us. Animals tend to lick wounds and utilize their saliva. The knowledge of using saliva as a compound that can accelerate wound healing comes from observing the behavior of these animals which is considered capable of triggering the wound healing process [6].

Based on several studies tested [1, 5, 7, 8], saliva is proven to be useful as a factor that can accelerate wound healing with topical application. Saliva is believed to be able to accelerate wound healing, especially in the proliferation phase, where it is related to the growth factors contained in saliva and plays a role in the regeneration of new Jernigan in the wound.

Wounds are form of skin tissue damage as a result of harmful contact with heat, sharp objects, medical procedures, or physiological changes. The wound healing process is complex and consists of several phases, namely hemostasis, inflammation, proliferation and remodeling. Things such as the incorporation of vascular responses, the formation of chemical compounds to support healing, and cellular activity are highly interrelated [9].

The wound healing process starts from bleeding, the body is able to activate hemostasis with the help of other components such as fibrinogen, fibrin, keratinocytes, and others. Hemostasis has a protective role in wound healing. During hemostasis, exudate-containing proteins are released to dilate blood vessels and release histatin which can facilitate the process of remodelling and re-epithelialization in wound healing.

In saliva, histatin is found to have important functions in the wound healing process. Histatin is an endogenous peptide found in saliva, known for its anti-microbial properties. Histatin has important roles in running biological systems in the body. The histatin content found in saliva is known to increase the migration and proliferation of keratinocytes. So that the wound healing process has the possibility to heal faster. Histatin consists of various types and uses, the most commonly found is Hst 1 which has been most recognized as a factor that can support wound healing in terms of proliferation [10].

Saliva also contained other growth factors hormone such as tranforming growth factor, fibroblast growth factor, insulin growth factor, and epidermal growth factor. These factors can encourage the body to accelerate wound healing, for example in inducing the proliferation of fibroblasts and keratinocytes [6].

From the information that has been described, this journal publication is intended to determine the effectiveness of saliva which is believed to accelerate wound healing.

2. Materials and methods

In the research journal conducted, we used the literature review method. The results of works and research that have been examined by researchers are systematically arranged in finding the results of the research discussed in this journal.

In the literature review that has been done, we use various sources of journals and research available on internet databases such as Google Scholar and various other sources that we can find through keyword searches such as saliva, wound healing, proliferation, and topical application. From the journals found, we have arranged them in such a way as to form a study that is relevant and able to cover the themes discussed in this journal.

3. Results

Prior investigations indicated that the experimental group exhibited notably accelerated wound healing rates compared over the control group at 3, 5 and 7 post-injury. The research suggests that Hst 1 facilitates wound stroma deposition and granulation filling in vivo, as evidenced by higher collagen fiber levels in wounds treated with Hst 1 compared to the control group at 3, 5 and 7 days post-injury. Furthermore, Hst 1 promotes the migration of fibroblasts and myofibroblasts transformation in vivo, as indicated by increased fibroblast numbers and myofibroblast transformation degree in Hst 1-treated wounds compared over the control group. Notably, α-SMA expression, a crucial myofibroblast marker, was higher for the Hst 1-treated group over the control group. However, there was no significant disparity in

TGF-β1 expression, a key factor in promoting fibroblast-to-myofibroblast transformation, between the control and Hst 1 treatment groups.

According to the research findings, it was demonstrated that Hst 1 enhanced the mechanical characteristics of skin wound closure by improving fiber arrangement and organization. This was evidenced by the observation that the skin treated with Hst 1 displayed a higher presence of collagen, reticular, and elastic fibers in the vicinity of the healed wound. Additionally, the healed skin in the Hst 1 group exhibited an increased proportion of type III collagen. [11].

4. Discussion

Saliva is an exocrine secretory liquid produced by the human salivary glands. Saliva is a colorless and intricate fluid with properties that promote wound healing and combat microbes. Within saliva, numerous biological compounds contribute to functions such as lubrication, antimicrobial action, antioxidant properties, inflammation regulation, immune response, and facilitation of wound healing. Additionally, saliva contains growth factors like Nerve Growth Factor (NGF) and Epidermal Growth Factor (EGF), which play a role in expediting the process of wound healing [5].

Wound healing is a multifaceted process characterized by several sequential phases as ordered from hemostasis, inflammation, proliferation, and remodeling. During the hemostasis phase, the wound is sealed through blood clotting, marking the initial step in the healing process. Platelet activation in this phase triggers the release of various cytokines, which play a crucial role in kickstarting healing by attracting inflammatory and resident cells through chemotactic signaling. This release of cytokines initiates an inflammatory response during the clotting phase, facilitating tissue debridement by eliminating damaged tissue and pathogens.

The inflammatory phase starts when neutrophils adhere to the endothelium shortly after trauma occured. Neutrophils with elastase and collagenase clear the way of migration towards the extracellular portion. Where cells will degrade protein matrix, phagocytose bacteria and attract additional neutrophils and macrophages. The most important inflammatory cells, macrophage cells, will dominate the wound area from day 3 to day 5. At 6-8 hours after wounding, damaged blood vessels will secrete plasma and neutrophils to the wound area. Neutrophils will start digesting and clearing cell debris and foreign cells so that neutrophils will undergo apoptosis and their role is replaced by macrophages.

The proliferation phase begins 24 hours after trauma and includes fibroplasia, granulation, epithelialization and angiogenesis. Fibrin matrix as a place of keratinocyte migration where some of these cells are stimulated by TGF- β which will move from the side of the wound and hair follicles to shift the keratinocytes that already exist around the wound area. At the same time VEGF induced by low oxygen promotes angiogenesis and influences capillary nearby the endothelial cells to be recruited and stimulated to proliferate. Platelet derived growth factor will regulate fibroblasts that move in 48 hours to 72 hours after the wound to proliferate the dermal matrix. The final phase is Remodeling where wound healing takes several weeks to years. The contraction of wound begins on day 5 due to a change in fibroblast phenotype to actin-laden myofibroblast. The contraction process will pull the wound edges closer together, covering the surface area and increasing the speed of wound closure [6].

Saliva is not only a factor that accelerates oral wound healing, but can also be used for cutaneous wound healing with good and faster wound surface reconstruction results. According to research conducted, saliva administration has an effect in accelerating the wound healing process with the best reconstruction results even though it is not significant in data analysis. EGF is also one of the important elements of saliva that functions to promote early healing of skin wounds, EGF is the best standard for accelerating diabetic wound healing. EGF also functions to spur cell differentiation, cell migration, and cell proliferation to accelerate wound healing with the best wound reconstruction [5].

Apart from Nerve Growth Factor (NGF) and Epidermal Growth Factor (EGF), saliva contains histatin protein, a low molecular weight peptide rich in histidine. Histatin is expressed in human saliva and higher primates. Currently, 26 types of histatins have been identified in saliva, with histatin 1, histatin 3, and histatin 5 constituting more than 80% of the total histatin concentration. Histatin is produced by the acini of serous glands, including the parotid, submandibular, and sublingual glands, which contribute to saliva production [9]. Research conducted by Shah [10] indicated that Hst5, similar to other histatin peptides, can enhance cell migration, demonstrating comparable effectiveness. Furthermore, akin to Hst1, Hst5 also exhibits favorable outcomes, promoting cell spreading.

Histatin exhibits the ability to enhance cell migration in oral epithelial cells also in various non-oral epithelial cell types, including corneal epithelial cells, skin epithelial cells, osteoblasts, fibroblasts, and endothelial cells [9]. This suggests that the presence of histatin protein in saliva holds promise for topical wound healing on the skin's surface.

Furthermore, research indicates that there is potential in human saliva to accelerate skin wound closure and trigger inflammatory responses without interfering normal epidermal differentiation. These observations carry significant clinical implications, as utilizing a patient's own saliva could offer a highly practical and cost-effective approach to enhancing wound closure [8].

It's established that wounds in the oral mucosa tend to heal faster effectively compared to skin wounds, with various factors influencing this discrepancy, vascularization, tissue structure, and presence of saliva [12]. The wound healing complex process involves interactions among fibroblasts, endothelial cells, epithelial cells, and other cell types. Initially recognized as an antibacterial agent, histatin gradually reveals multiple biological effects crucial for wound healing, such as facilitating epithelial cells and fibroblasts to migrating, angiogenesis promotion, and enhancing the re-epithelialization process. Histatin plays a role in the proliferation stage and inflammatory response during wound healing. Beyond its impact on epithelial cell migration, histatins also influence cell adhesion. Research demonstrates that histatin 1 enhances the elongation and adhesion of human retinaldehyde pigment epithelial cells and human intestinal epithelial cells, with effective concentrations ranging from 1 μM to 10 μM. Regarding fibroblasts, histatin affects their proliferation and migration. Specifically, fibroblast migration is observed after 96 hours of histatin incubation, with no significant increase observed with prolonged exposure. This suggests that histatin exerts its greatest influence of administration on fibroblast migration in 8 hours, with the effect persisting for up to 96 hours even after the removal of the protein [9].

5. Conclusion

Based on the journal studied, topical application of saliva to wounds has a good effect in accelerating wound healing due to various biological substances contained in saliva that function in antimicrobial and antioxidant activity, inflammatory, lubrication, and immune responses. The content of histatin which are growth factors such as Nerve Growth Factor (NGF) and Epidermal Growth Factor (EGF) contained in saliva can also function to accelerate wound healing. In addition to wounds in the oral cavity, saliva can also stimulate wound closure on the skin. In conclusion, saliva is effective in accelerating wound healing and also has the potential to become a new therapy for treating open skin wounds.

Compliance with ethical standards

Acknowledgments

The authors thank the reviewers for their valuable contributions in checking and providing very meaningful feedback on this journal.

Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this document.

References

[1] Lesmana, D., Tjahajawati, S. and Lubis, V.T., 2016. Saliva as a Potential Diagnostic of Biomarker of Oral and Systemic Diseases: Saliva Sebagai Biomarker Potensial Diagnostik Penyakit Rongga Mulut Dan Sistemik. *Dentika: Dental Journal*, *19*(2).

[2] Ilea, A., Andrei, V., Feurdean, C.N., Băbţan, A.M., Petrescu, N.B., Câmpian, R.S., Boşca, A.B., Ciui, B., Tertiş, M., Săndulescu, R. and Cristea, C., 2019. Saliva, a magic biofluid available for multilevel assessment and a mirror of general health—A systematic review. Biosensors, 9(1), p.27.

[3] Goswami, Y., Mishra, R., Agrawal, A.P. and Agrawal, L.A., 2015. Salivary biomarkers: A review of powerful diagnostic tool. IOSR J. Dental Med. Sci, 14(3), pp.80-87

[4] Vila, T., Rizk, A.M., Sultan, A.S. and Jabra-Rizk, M.A., 2019. The power of saliva: Antimicrobial and beyond. *PLoS pathogens*, *15*(11), p.e1008058.

[5] Wahyudi IA, Magista M, Angel M. Efektivitas Penggunaan Saliva Dibandingkan Povidin-Iodin 10% Terhadap Penyembuhan Luka Pada Kutaneus Tikus Sprague Dawley. *J Biomedika*. 2013;2(1):1-13.

[6] Azizah SN, Mustajib M, Agustiar AB, Akmalia HA. Kajian Etnosains Pada Potensi Penggunaan Saliva untuk Penyembuhan Luka Ringan di Lampung. *Al-Hayat J Biol Appl Biol*. 2021;4(1):43-54.

[7] Putro, B.C. and Dachlan, I., 2018. The effect of human saliva compared to Aloe vera on wound healing of 2nd degree burn injury in animal models. *J Med Sci*, *50*(4), pp.376-384.

[8] Neves R, Buskermolen J, Roffel S. Human saliva stimulates skin and oral wound healing in vitro. J Tissue Eng Regen Med. 2019;13:1079–1092.

[9] Pan L, Zhang X, Gao Q. Effects and mechanisms of histatins as novel skin wound-healing agents. *J Tissue Viability*. 2021;30(2):190-195.

[10] Shah D, Son KN, Kalmodia S, et al. Wound Healing Properties of Histatin-5 and Identification of a Functional Domain Required for Histatin-5-Induced Cell Migration. *Mol Ther - Methods Clin Dev*. 2020;17(June):709-716.

[11] Cheng L, Lei X, Yang Z, et al. Histatin 1 enhanced the speed and quality of wound healing through regulating the behaviour of fibroblast. Cell Prolif. 2021;54:e13087.

[12] Torres P, Castro M, Reyes M, Torres VA. Histatins, wound healing, and cell migration. Oral Dis. 2018;24:1150–1160.

[13] Saputra, R. and Rahman, S., 2022. Penatalaksanaan Adenoma Pleomorfik Kelenjar Liur Minor Palatum. Jurnal Otorinolaringologi Kepala dan Leher Indonesia, 1(1).

[14] Purnama, H., Sriwidodo, R.S. and Ratnawulan, S., 2017. Review sistematik: proses penyembuhan dan perawatan luka. Farmaka, 15(2), pp.251-256.